Featuring...

Kaspar Locher

Winner of the 2008 *FEBS Letters* Young Scientist Award

Dr. Kaspar Locher was selected as the winner of the 2008 *FEBS Letters* Young Scientist Award for his outstanding work and paper on the "Structure of the multidrug ABC transporter Sav1866 from *Staphylococcus aureus* in complex with AMP-PNP". Assistant Professor of Molecular Membrane Biology at the ETH in Zurich, Switzerland, Kaspar Locher is a dynamic young group leader with a restless mind and a resolute personality.

What are ABC transporters and why did you choose to study them?

ABC transporters are one of the most diverse families of transport proteins in biology. Somebody called them "Nature's favorite pump". ABC importers can take ATP from the cell and convert it into mechanical force to drive nutrient intake in bacteria, while ABC exporters extrude toxic substances in bacteria, in cancer cells (a major cause of multidrug resistance in chemotherapy), or in epithelial cells of the blood-brain barrier, to protect the brain from toxic insults.

Membrane proteins have been the object of my studies ever since my PhD, when I determined the structure of an iron transporter in the outer membrane of *Escherichia coli* [1]. I am fascinated by the diversity of functions transporters can have, and I am tickled by their resistance to crystallization. I can't resist the challenge, I just have to crack the problem!

Why are membrane proteins so difficult to crystallize?

The natural habitat of these proteins is the membrane, which is composed by lipids. In order to obtain crystals, the lipids need to be removed by detergents, which, however, create a jelly-like torus around the protein as a side effect. In these conditions, the protein cannot easily make strong lattice contacts during the process of crystallization. In addition, the same forces that hold the protein in the lipid bilayer also hold the protein core together. Detergents therefore have a very destabilizing effect on membrane proteins.

In order to solve the structure of an ABC exporter, we had to screen for the most stable homolog, which would behave best during the purification and crystallization process. The choice fell on Sav1866 from *S. aureus*.

What is the *FEBS Letters* award-winning paper about?

Our recent publication on the full structure of Sav1866 [2], which is the first high resolution structure of an ABC exporter, opened an important point of discussion that needed to be clarified. Although the structure was obtained in complex with ADP, it reflected an outward-facing conformation of the transmembrane domains coupled to a closed conformation of the nucleotide-binding domains, typical of the ATP-bound state. The results were very convincing but for the one missing phosphate, raising questions about the physiological relevance of our findings. In the study published in *FEBS Letters* [3], we solved the structure of Sav1866 bound to AMP-PNP, a non-hydrolyzable analogue of ATP. The structure matched the one obtained with ADP, suggesting that in its natural environment Sav1866 couples an ATP-bound state to a drug-releasing outward conformation.

How are you planning to crystallize the inward-facing conformation?

This is proving to be a tough problem. We are trying to crystallize it without ADP or ATP, or to force the inward-facing conformation by mutating specific domains of the protein. However, Sav1866 seems to be very stable in the outward-facing conformation, even in the absence of a ligand, and neither of these strategies has worked so far. We will probably have to search for another homolog in nature that is relatively stable in the inward-facing conformation.

Why did you choose *FEBS Letters* to publish this paper?

Our work is not a large biochemical study, but it proves an important point, of the sort that you would find in *FEBS Letters*. We knew it would get a fast and fair review, which is what we needed, since the main part of the study had been accepted in *Nature*. I like *FEBS Letters*.

In your opinion, what makes a good scientist?

Enthusiasm, stubbornness, and caution. We need that to stay up at night to work at the synchrotron, and give up weekends or cut down on vacation. We do not like to give up and we want to understand. A scientist's job can be frustrating and fascinating at the same time. Experiments often need to be repeated dozens of times before they give good results. Sometimes, after two years of hard work, you just have to accept that a project is not going anywhere. In these cases, I like to quote the Nobel Laureate Rod MacKinnon, who once said: "I would rather fail trying than never try at all".

If you had unlimited funds and expertise, which other field of science would you like to explore?

I would like to understand awareness from the molecular point of view. However, this is an extremely vast field that Neurobiologists are only beginning to uncover. A full understanding of awareness is unlikely to be achieved within my lifetime, whereas I am confident that the transport phenomena we're studying will be understood.

References

[1] Locher, K.P. et al. (1998) Cell 95 (6), 771–778.
[2] Dawson, R.J. et al. (2006) Nature 443 (7108), 180–185.
[3] Dawson, R.J. et al. (2007) FEBS Letters 581 (5), 935–938.

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